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Proposal of a New Grading System for Malignant Fibrous Histiocytomas

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Abstract. *The proposed grading system for malignant fibrous histiocytomas (MFH) comprises 3 grades of malignancy. Analogous to other grading systems, the system includes the factors of mitotic rate and necrosis. In addition to these two factors, the concept of cellularity was included. The prognostic relevance of the grading systems published by Costa, Coindre, van Unnik, Pezzi and Tsujimoto as well as the grading system proposed by the present study was tested on 161 MFH. The results showed that all grading systems tested produced clearly significant differences ($p<0.01$) with regard to the survival estimated for patients with various grades of malignancy. These results revealed the superiority of systems that use 3 grades of malignancy over a 2-grade classification. The proposed grading system yielded a lower percentage of grade II tumours (37%) than the grading systems of Coindre (60%) and van Unnik (70%). In the multivariate analysis of all grading systems, the proposed grading system was the only one to show prognostic relevance ($p<0.05$).*

Not only the subtype classification, but also other histopathological features can also be helpful in establishing the prognosis and the therapeutic strategy for each individual tumour (1-2). The parameters for grading malignant soft tissue tumours recommended by the International Union Against Cancer (UICC) include cellularity, pleomorphy, mitotic activity and necrosis. Several of these histopathological parameters have been combined to form grading systems (3-11).

Many of these gradings have proven their prognostic validity. Nonetheless, there is little agreement as to which grading systems are the most reliable for malignant soft tissue tumours. It is fundamentally accepted that grading factors (such as the number of mitoses per visual field) in relation to tumour type and subtype can have an entirely different prognostic validity. The major and most widespread grading systems of North America and Europe are those of the National Cancer Institute, the grading system of the French Federation of Cancer Centers and that used by the European Organization for Cancer Research (EORTC) (5,6,12). The prognostic relevance of these grading systems has been demonstrated in heterogenous samples of various types of soft tissue sarcoma (12,13). In contrast, controversial discussions have also focused on the question of how to select a suitable grading system for malignant fibrous histiocytomas (MFH) (13).

Within the context of these discussions, the general opinion is that grading systems that have indeed become established for other malignant soft tissue tumours do not correlate with the metastatic potential of MFH (5,14-16). Suprisingly enough, large-scale studies, that have combined several accepted grading parameters in a thoroughly ill-defined manner and which have considered only one single grading parameter, have found a highly significant correlation between tumour grading and parameters of survival (8,17).

One of the more recent studies has shown that the defined grading system of the French Federation of Cancer Centers is the most important prognostic parameter for disease-specific and metastasis-free survival (6,18).

The main objective of this investigation was to present a new histopathological grading system for MFH and to

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compare the prognostic relevance of this new system with existing grading systems.

Materials and Methods

A total of 161 cases of MFH supplied from the archives of the Pathological Institute of the University of Göttingen, Germany (1991-1994; 44 cases) and from the Pathological Institute of the University of Krakow, Poland (1986-1994; 117 cases) were investigated. Seventy-two (45%) patients with MFH were women and 89 (55%) men. The age of the patients ranged between 4 and 90 years (mean 61 years).

The localisation of the investigated tumours was distributed over the following anatomical regions: head and neck (n=27; 17%), upper extremities (n=19; 12%), lower extremities (n=86; 53%) and trunk (n=29; 18%). Thirty-six of the tumours (22%) showed superficial localisation, 117 (73%) deep localisation. The tumour depth could not be determined in 8 tumours. Tumour size varied between 0.7 and 36 cm (median tumour diameter 8 cm). Thirty-nine (24%) of the tumours were assigned to the category pT1, and 122 (76%) of the tumours were in stage pT2. In 7 tumours, the tumour size (and/or the pT stage) could not be determined. In 43 patients (27%) distant metastases were clinically present at the time of primary diagnosis. In 2 patients, locoregional lymph node metastases were validated by histology. All patients were observed from the time of diagnosis up to the end of the study period (October 2001), and disease-related survival within this period was documented. Non-MFH-related fatalities were excluded from the investigation. Ethical aspects of this study were proven at the Ethical Center of Adam Mickiewicz University in Poznan, Poland.

The tumour tissue from the archives of the Pathological Institute of the University Göttingen and from the Pathological Institute of the University of Krakow were routinely fixed in 3.6% formaldehyde and embedded in Paraplast. Serial sections 3 μm thick were prepared from all investigated tumours. The tumours were subtyped according to the criteria of the international histological classification for soft tissue tumours, taking the detailed description by Enzinger and Weiss into consideration (14,15). Accordingly, 113 cases (70%) were classified as storiform-pleomorphic subtype, 28 (17%) as myxoid subtype, 11 (7%) as inflammatory subtype and 9 (6%) as giant cell tumour.

Application of published grading systems. Published grading systems were used to determine the histopathological grade of malignancy in freshly cut and H.E.-stained histological specimens (Figure 1). One to 9 histological specimens were available from each tumour, in accordance with the number of paraffin blocks. The histopathological grade of malignacy was assessed according to the published methods of Costa, Coindre and Pezzi and based on a method described by Tsujimoto (5-8). Grading parameters on which the applied grading systems are based comprised the number of mitoses per area, cellularity, the surface area of necrosis and differentiation (5-8,12). Tumour differentiation in the investigated MFH was defined as constant (reliable typing, score 2) because, by definition, there was no similarity to normal tissue in MFH and tumours without MFH-typical morphological differentiation, and/or unreliably typed tumours were excluded from the study. Cellularity was defined as a high cell content (more than 50% of the tumour surface), according to the typically high cell content in inflammatory MFH or MFH of the giant cell type, average cell content (20-50% the tumour surface) and low cell content (less than 20% the tumour surface according to the findings in myxoid MFH). For determination of the mitotic count per area, the portion of the tumour with the highest mitotic rate was sought and examined in that area with at least 10 high-power fields. If the mitotic rate was low (0-6 mitoses), 20 to 50 high-power fields were used for determining the mitotic rate. The histopathological grade of malignancy was established for each tumour based on the individually determined grading parameters. For each grading system, the percentage of tumours of a malignancy grade, median patient survival with tumours of a malignancy grade and differences in survival between the grades of malignancy were calculated and plotted as Kaplan-Meier curves (19).

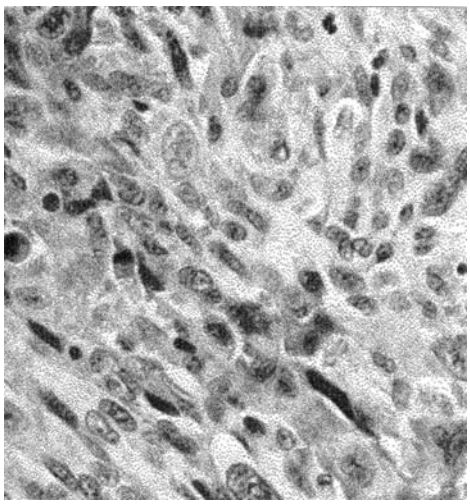

Figure 1. *HE-stained case diagnosed as malignant fibrous histiocytoma with typical morphology.*

Development of a new grading system. In addition to the published grading systems described above, a new grading system was introduced. Besides the grading parameters used by Coindre and van Unnik, namely necrosis and mitosis, the parameter of cellularity was considered in the proposed grading system since it correlates with MFH subtyping more closely than necroses and mitoses (*e.g.* myxoid *versus* non-myxoid) and better reflects the biologically relevant expression of oncogenes and tumour suppressor genes of MFH (6-12). The grade of malignancy (I-III) was determined using a score that was made up as follows: mitoses 1=0-9, 2=10-19, 3=>19/10 HPF), necroses (0=0%, 1=1-50%, 2=51-100%) and cellularity (1-3). (Score 2-3=grade I, Score 4-5=grade II, Score 6-8=grade III) (Table I). The histopathological grade of malignancy was determined for each tumour according to the proposed grading system. The results obtained with the proposed grading system were compared with those obtained after applying the published grading systems with regard to the following parameters: percentage of the tumours of each individual grade of malignancy in the overall tumour sample, percentage of patients alive (censured) or dead at the end of the observation period, survival percentile for each grade of malignancy, significance of the differences in the survival between individual grades of malignancy and Kaplan-Meier curves.

Table I. *Parameters included in the grading system according to Brinck (the present study).*

Parameter	Score	
1. Mitotic activity	1	0-9/10 HPF*
	2	10-19/10 HPF
	3	greater than 19/10 HPF
2. Necrosis	0	Lacking
	1	up to 50%
	2	more than 50%
3. Cellularity	1	low cell content
	2	medium cell content
	3	high cell content

MFH grade I: Score 2-3; MFH grade II: Score 4-5; MFH grade III: Score 6-8.
• 1 HPF = 0.19635 mm^2

Results

Published grading systems. The grading systems of Costa, Pezzi and Tsujimoto are all based on single grading parameters and differentiated between two grades of malignancy (low-grade and high-grade and/or grades II and III) (5-8).

Following application of the grading system of Costa, 70% of the tumours were classified as malignancy grade II (median survival 32 months) and 30% of the cases as malignancy grade III (median survival 11 months). The differences in survival between grade II and grade III were highly significant ($p<0.01$) (Figure 2A).

Following application of Pezzi's histological grading system, 44% of the tumours were classified as malignancy grade II (median survival 62 months) and 56% as malignancy grade III (median survival 14 months). The differences in survival between grade II and grade III were highly significant ($p<0.01$) (Figure 2B).

Delineation of low and high-proliferating tumours according to the criteria of Tsujimoto produced 30% low-proliferating tumours (median survival 78 months) and 70% high-proliferating tumours (median survival 18 months). The differences in survival between grade II and grade III were highly significant ($p<0.01$) (Figure 2C).

The grading systems of van Unnik and Coindre distinguish between three grades of malignancy (6,12). Coindre's grading system classified 21% as grade I tumours (median survival was not reached), 60% as grade II tumours (median survival 10 months). The differences in survival between grade I and grade II as well as between grade II and grade III tumours were highly statistically significant ($p<0.01$) (Figure 2D). Based on the grading system of van Unnik the percentage of grade I tumours was 17% (median survival was not reached), of grade II tumours 70% (median survival 21 months) and of grade III tumours 13% (median survival 10 months).The differences in survival between grades I and II as well as between grade II and grade III tumours were highly statistically significant ($p<0.01$) (Figure 2E).

The proposed grading system. The application of the proposed grading system produced 19% grade I tumours, 37% grade II tumours and 44% grade III tumours. The median survival for MFH with grade of malignancy I was not achieved, with grade of malignancy II was 36 months and with grade of malignancy III 11 months. The differences in survival between grades I and II, and between grade II and grade III tumours were statistically highly significant ($p<0.01$) (Figure 2F).

Predictability of survival based on the grading systems. Successive inclusion of the grading systems according to Costa , Pezzi, Tsujimoto, Coindre and van Unnik, as well as the proposed grading system, showed that the proposed grading system was statistically best suited for predicting survival (5-12).

In conclusion, Cox regression indicated that the proposed grading system most effectively predicts survival. Other grading systems provide no additional or statistically valuable information (Table II).

Discussion

The present study investigated 161 cases of MFH provided by the Pathological Institutes of the University of Göttingen and the University of Krakow. The processed tumor samples belong to one of the larger published MFH series that has been examined utilizing special techniques. The patient samples of other authors, *i.e.* Weiss and Enzinger, Pezzi, Hashimoto and Doussal, were more extensive, but were investigated with regard only to the prognostic relevance of grading parameters (8, 15-18). The study presented here presents a proposed grading system for MFH which is based on the 3 grading parameters of cellularity, mitotic index and extent of necroses. This grading differs from the other grading systems in that these 3 prognostic parameters, the prognostic relevance of which has been demonstrated with regard to cellularity by Pezzi and with regard to mitotic index and necroses by Doussal, were combined together for the first time (8,18). The advantage of this newly presented grading system is that the cellularity parameter varies depending on the MFH subtype. The prognostically favourable myxoid variant typically shows low cellularity. The prognostic relevance of the proposed grading system derives from the fact that when the probability of survival of all grading systems applied in the multivariate analyses was compared, the

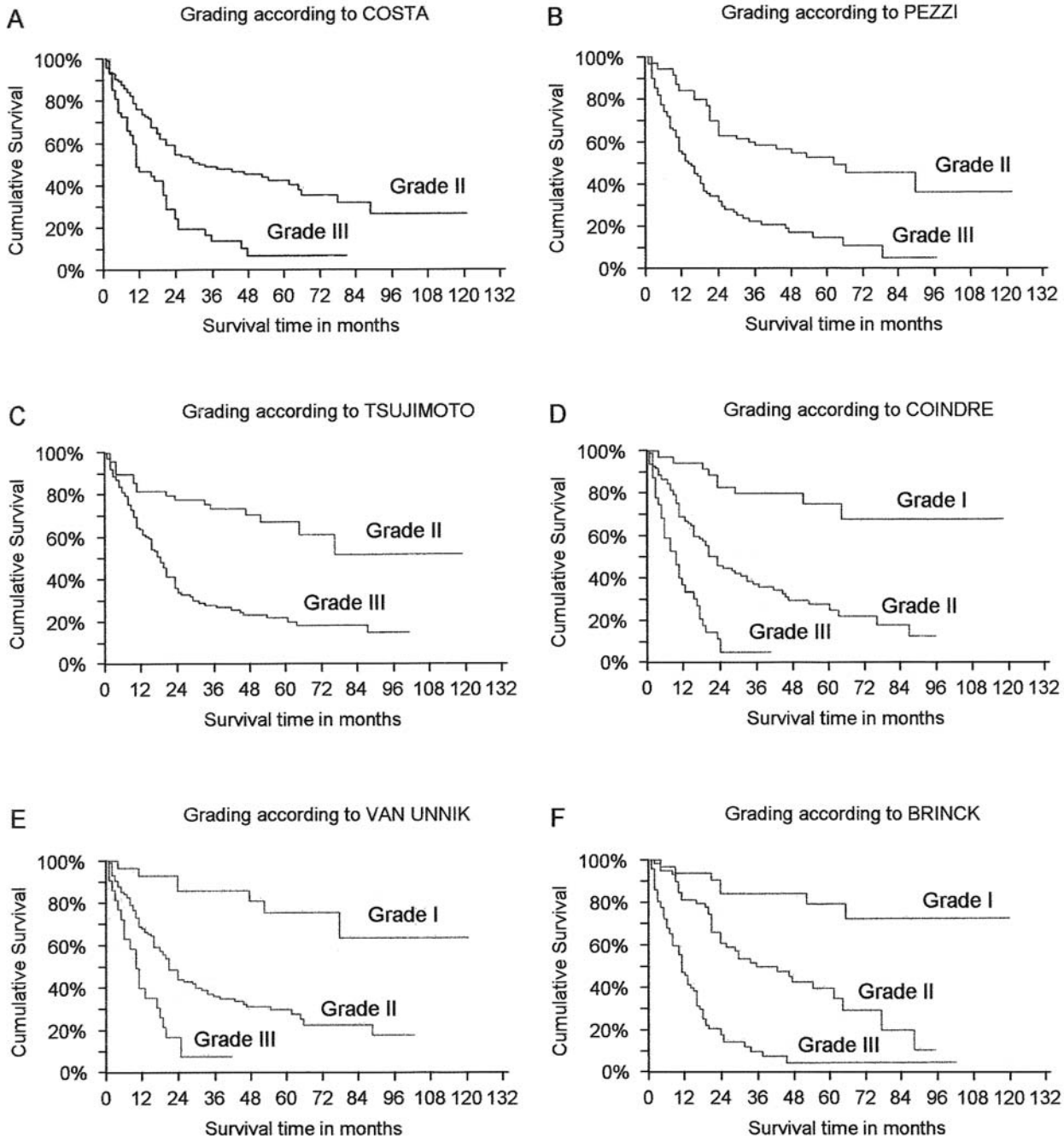

Figure 2. *A. Kaplan-Meier survival curves of malignant fibrous histiocytomas graded according to Costa. B. Kaplan-Meier survival curves of malignant fibrous histiocytomas graded according to Pezzi. C. Kaplan-Meier survival curves of malignant fibrous histiocytomas graded according to Tsujimoto. D. Kaplan-Meier survival curves of malignant fibrous histiocytomas graded according to Coindre. E. Kaplan-Meier survival curves of malignant fibrous histiocytomas graded according to van Unnik. F. Kaplan-Meier survival curves of malignant fibrous histiocytomas graded according to Brinck.*

proposed grading system had an independent influence on probability of survival.

Discussions have long revolved around the question as to whether a double or triple grading system has greater prognostic validity for MFH. The results of these discussions are reflected in the structure of the various grading systems. The grading system of the National Cancer Institute (USA) proposed by Costa distinguishes between MFH of malignancy grades II and III. The same applies to the grading system of Pezzi (5,8). In contrast, the grading systems more established

Table II. *Explorative results of Cox regression for predicting survival from all grading systems*

Forward parameter selection

Prognostically independent factors staying in a model	Regression coefficient	*p*-value	Change of risk of death	Confidence interval	
Proposed grading	$p<0.001$				
Proposed grading I *vs.* III	-1.36	$p<0.001$	-74.3%	-84.7%	-56.7%
Proposed grading II *vs.* III	0.06	$p=0.746$	5.8%	-24.7%	48.5%

Backward parameter selection

Prognostically independent factors staying in a model	Regression coefficient	*p*-value	Change of risk of death	Confidence interval	
Proposed grading	$p<0.001$				
Proposed grading I *vs.* III	-1.15	$p<0.001$	-68.4%	-81.8%	-45.3%
Proposed grading II *vs.* III	0.05	$p=0.773$	5.2%	-25.5%	48.6%

in Europe, namely those of Coindre and of EORTC (van Unnik), use a 3-level classification of MFH (6,12). Testing of the prognostic relevance of the aforementioned grading systems and the proposed 3-level grading system yielded significant differences ($p<0.001$) in survival between patients with tumours of varying grades of malignancy for all grading systems. These results prove the advantage of a grading system with 3 grades of malignancy.

Caution is advised, however, should one attempt to compare the practical grading classifications of various systems. From the theoretical standpoint alone, it is not possible to prognostically equate tumours that have been allocated to the same grade of malignancy, but according to different systems. For appropriate prognostic classification of a tumour, apart from its grading, it is above all important to consider the pTNM stage. The multivariate analyses conducted for this purpose showed that the proposed grading system and tumour size are independent prognostic parameters. Similar statistical interrelationships were verified by Doussal for Coindre's grading of MFH (6,18). In order to test the prognostic relevance of the proposed grading system in connection with the parameters of the UICC's TNM system, the proposed grading system was integrated into the staging recommended by the UICC for malignant soft tissue tumours (20).

Based on the experience and evidence gained with the present work, it is indeed feasible in practice to define (delineate) MFH with relatively good prognosis (*e.g.* myxoid tumours of malignancy grade I) as opposed to patients with poor prognosis (*e.g.* high-proliferating tumours with aneuploid status and the possible presence of significant necroses >10%). However, an intermediate group will always remain that can neither be assigned to malignancy grades I nor III, and the prognosis of which should be regarded as difficult to establish.

Since the type of systemic therapy to be given to the individual patient with MFH largely depends on the grade of malignancy, the proposed grading system presented here should become the method of choice.

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